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THE POSTRESUSCITATION PATIENT: VENTILATION AND
METABOLISM(U) COLUMBIA UNIV NEW YORK DEPT OF SURGERY
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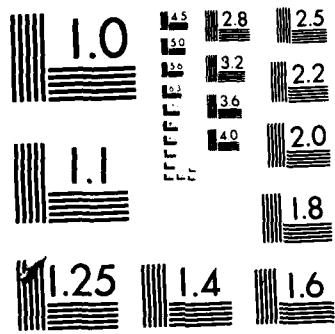
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Contract # DAMD17-81-C-1048

October 1, 1980 - September 30, 1981

U.S. ARMY RESEARCH & DEVELOPMENT COMMAND

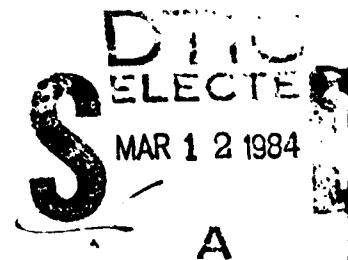
John M. Kinney, M.D.
Principal Investigator

Department of Surgery
College of Physicians and Surgeons
Columbia University
New York City

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I PUBLICATIONS

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1. Askanazi J, Rosenbaum SH, Michelsen CB, Elwyn DH, Hyman AI, Kinney JM:
Increased body temperature secondary to total parenteral nutrition.
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II EFFECTS OF NUTRITION AND INJURY ON VENTILATION.

A. Ventilatory studies in injured and depleted patients. Our previous studies with total parenteral nutrition have largely been based on a mixture of hypotonic glucose and amino acids which our group has shown to cause a significant increase in CO₂ output. An associated increase in oxygen consumption indicating increased energy expenditure, does not occur in patients with nutritional depletion but does occur, superimposed on whatever level of hypermetabolism is present, if the patient is acutely injured or has a serious infection. Last year, we proposed to examine this problem by studying three groups of patients: normal convalescents following colon resection; normal convalescents following total hip replacement; and patients with major accidental injury. It was planned that within 48 hours following operation or injury the patients would be randomly assigned to receive 5% dextrose 20% dextrose or 20% dextrose plus amino acids. Various ventilatory measurements would be made at 6, 24 and 48 hours after starting the intravenous nutrition.

During January of 1981, these studies were begun, after completing a study of 6 depleted surgical patients whose ventilatory response to CO₂ was studied while receiving 5% dextrose and again after 7 days of either of two hypercaloric intravenous diets providing energy equal to 1.5 times the REE and either 12 or 24 gms of amino acid nitrogen per day. The order of administration of the high and low nitrogen diets were randomized. Typical results are plotted for 6 patients in Figure 1. During the 5% dextrose infusions, these patients were less sensitive to CO₂ than normal subjects. The effect of the low nitrogen total parenteral nutrition (TPN) was to increase the sensitivity of the patient to CO₂, an effect which was more marked

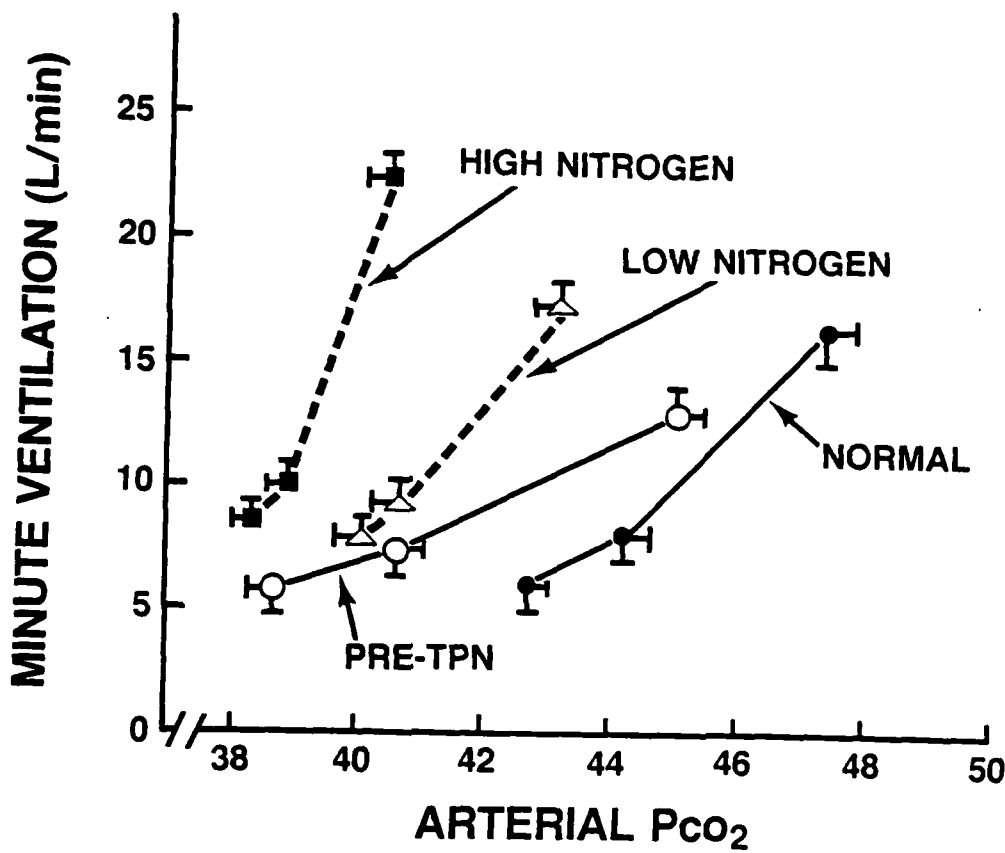


Figure 1

after 7 days of the high nitrogen intake.

Studies of acutely injured patients were begun with the administration of TPN to a young healthy male 3 days after receiving multiple gunshot wounds to the abdomen. He had extensive peritoneal contamination from multiple bullet wounds to the intestinal tract which were treated at emergency laparotomy with primary closure. He ran a low grade fever during the first postoperative week but then had a successful convalescence. Because of the probability of intraperitoneal sepsis, and prolonged delay in the use of his intestinal tract, he was started on TPN on his third postinjury day. His minute ventilation showed a dramatic response to TPN. On 5 % dextrose it was 8 and 10 l/min on room air and 2% CO_2 respectively. On TPN these values doubled to 16 and 20 l/min.

B. Effects of mouth piece and noseclip and of postural position on the respiratory response to CO₂. It seemed to us that our studies on depleted patients and our studies with this gunshot victim indicated that carbohydrate infusion was stimulating hyperventilation mainly by increasing CO₂ production, while administration of amino acids was stimulating ventilation by an entirely different mechanism, perhaps by increasing the sensitivity of the ventilatory center to CO₂. These studies were reviewed with Dr. Joseph Milic-Emili, Professor of Physiology at McGill University and an international authority on the control of breathing. Dr. Milic-Emili found the studies to be extremely provocative but emphasized that we needed further validation of our non-invasive system for measurement of gas exchange for use in spirometric studies. Our previous published validation was only with resting normal subjects and did not include CO₂ response curves using conventional equipment (mouthpiece and noseclip) in the same individuals who were studied in the canopy. He also thought that we must show the different effects of the supine and sitting position on respiration in normal man, in order for our data to allow quick comparison with studies in the literature. He also reviewed our plans for the years work on ventilation and metabolism and observed that our experimental design would allow no definition of the effect of amino acids given alone. Therefore, studies were undertaken to examine the influence of the mouthpiece and noseclip compared with the canopy in studying the CO₂ response in normal subjects and patients. A study of 8 supine male subjects and 6 patients has been completed during this contract year.

In random order, 8 supine normal subjects and 6 patients convalescing from major abdominal operations, with mean body surface areas of 1.88 and 1.70 respectively were studied in the canopy with a (a) mouthpiece plus

noseclip and (b) without any attachment to the face or airway. Ventilatory patterns were assessed during room air breathing and during the administration of 2% and 4% CO₂. Measurements were made over a 10 minute period once stable levels of oxygen consumption and carbon dioxide production had been achieved. Ventilation (\dot{V}_E), tidal volume (V_T), frequency (f), inspiratory and expiratory times (T_I, T_E) and peak inspiratory and expiratory flows were measured. Mean inspiratory and expiratory flows (V_T/T_I, V_T/T_E) and inspiratory duty cycle (T_I/T_{TOT}) were calculated.

Normal subjects showed a relatively predictable increase in \dot{V}_E , V_T and V_T/T_I with the use of a MP + NC (Table I). Patients showed a more variable and unpredictable response to a mouthpiece plus noseclip.

Table I

NORMALS (n = 8)

		\dot{V}_E (ml/min)	V _T (ml)	f (min ⁻¹)	V _T /T _I (ml/sec)	T _I / T _{TOT}
CANOPY	RA	5.6	379	16	254	.38
	2% CO ₂	7.0	471	16	304	.39
	4% CO ₂	12.3	716	17	511	.41
MP+NC	RA	6.7*	444*	17	292*	.38
	2% CO ₂	8.0*	488	17	317*	.40
	4% CO ₂	13.8	761	18	559	.42

PATIENTS (n = 6)

CANOPY	RA	6.5	277	23	257	.39
	2% CO ₂	8.9	383	22	322	.41
	4% CO ₂	13.1	593	22	504	.42
MP+NC	RA	6.0	271	21	293	.41
	2% CO ₂	8.5	396	21	343	.41
	4% CO ₂	12.1	548	22	482	.42

Values are means; * significantly different from measurements with canopy alone (p<.05).

Previous studies have shown that a mouthpiece plus noseclip increased V_T 16-29%, and \dot{V}_E 14-31% in normal subjects breathing room air. In the present study ventilatory apparatus induced an increase in minute ventilation during both room air and stimulated breathing in normal subjects. These increases in ventilation are due to increases in tidal volume secondary to increases in mean inspiratory flow. In the surgical patients, the mouthpiece plus noseclip failed to induce any consistant changes in breathing patterns.

The surgical patients had higher frequencies and lower tidal volumes at rest, as has been previously reported. The response to CO_2 as measured by changes in \dot{V}_E was similar in patients and normals. While breathing CO_2 the characteristic changes induced by a mouthpiece plus noseclip were observed in normal subjects but not in patients. The changes in the control of breathing which led to a high f and decreased V_T in the patients may have attenuated the stimulus of the mouthpiece plus noseclip. Thus, the MP+NC had a predictable effect on breathing in normal subjects, while in patients it had a variable and less predictable effect. This data has important implications for studies of control of breathing in both normal subjects and surgical patients.

In order to meet the other question of Dr. Milic-Emili, regarding validation of our equipment, nine normal subjects have been studied in both the supine and seated position while breathing room air and during the administration of 2 and 4% CO_2 . The minute ventilation was 21% higher in the sitting position, and the tidal volume and mean inspiratory flow rates were also greater. When the relationship between minute ventilation and mean inspiratory flow was examined the ratio was always higher in the

seated position. No difference in response to CO₂ was seen when minute ventilation was compared with arterial PCO₂ or when mean inspiratory flow was compared with arterial PCO₂. However, the arterial PCO₂ in the supine position was significantly higher than in the seated position for every level of ventilation.

C. Effect of dextrose and amino acids on ventilatory chemosensitivity.

Our studies aimed at understanding the influence of intravenous glucose and intravenous amino acids when administered separately to normal and hyper-metabolic surgical patients have made good progress during this year.

In order to isolate the influence of glucose from the influence of amino acids in total parenteral nutrition, 4 healthy volunteer subjects were hospitalized and given intravenous glucose at either 281 kcal/m²/24hr or 1125 kcal/m²/24hr for 3 days each in random order. On the third day of each diet, ventilation and gas exchange were measured with room air, and following the administration of 2 and 4% CO₂. Arterial blood gases were sampled during each measurement. Ventilatory chemosensitivity to CO₂ was calculated as $\Delta V_E / \Delta P_{aCO_2}$ during CO₂ inhalation. High glucose infusion, while breathing room air, caused increases of 23% in minute ventilation, 27% in tidal volume, 12% in inspiratory flow rate and 13% in CO₂ production, as compared to values obtained with the low glucose infusion rate. Oxygen consumption and respiratory frequency were unchanged between the two levels of glucose infusion and there was no difference in ventilatory chemo-sensitivity. Therefore, in normal subjects, the increase in minute ventilation associated with glucose intake appears to be secondary to the increase in CO₂ (due to increasing RQ) but no change occurs in the behavior of the respiratory center to this increase in CO₂ production. To further

investigate the effect of nutrients on ventilation and examine the correlation between resting energy expenditure and chemosensitivity the effects of isotonic amino acid (AA) infusions by peripheral vein on O₂ consumption, CO₂ production and the ventilatory response to CO₂ were studied. The effects of a four hour amino acid infusion were studied in convalescing surgical patients and the data compared to that observed in normal subjects.

Six normal subjects (Group I) and five patients (Group II) convalescing from major surgery were studied. In group I, CO₂ responses were assessed after an overnight fast (control) and following 4 hours of an infusion of 125 ml/hr of an isotonic amino acid solution (AA4), via peripheral vein (Aminosyn 3.5%).

The patients all had infusions of 5% dextrose for 24 hours or more followed by identical infusions of isotonic AA for 4 hours (AA4). The response to CO₂ was evaluated prior to and after 4 hours of amino acids.

The normal subjects had a 54% ($p < .05$) increase in ventilatory sensitivity as measured by the change in VE/change in PaCO₂ during CO₂ administration. This was associated with an 11% increase in resting energy expenditure (REE). The patients had an 84% increase in chemosensitivity with a 2% increase in REE (Table II).

Isotonic amino acids administered in the postabsorptive state to normal subjects increase sensitivity to CO₂ within 4 hours. This affect does not appear to be due to changes in pH, but is associated to changes in metabolic rate in normals. The patients had a proportionally greater increase in ventilatory sensitivity than energy expenditure with the amino acid infusions. This indicates that an increase in metabolic rate may not entirely explain the phenomenon.

Table II

GROUP I

Normal Subjects (n=6)

	\dot{V}_E <u>PaCO₂</u> (1/torr- CO ₂)	VT/TI <u>PaCO₂</u> (ml/sec torr CO ₂)	REE (kcal/24* hour)	HC ₀₃ meq 1
Control	2.2 + 1.2	65 + 56	1302 + 410	26 + 2
AA4	3.4 + 2.0	110 + 60	1441 + 399	25 + 2

GROUP II

Patients (n=5)

Control	3.2 + 1.2	131 + 100	1501 + 283	27 + 3
AA4	6.0 + 4.9	230 + 190	1536 + 210	27 + 2

all values are mean + SD

*calculated from VO₂, VCO₂ and RQ

These results suggest that peripheral infusions of amino acids enhance ventilatory drive as measured by the response to CO₂ after four hours of infusion. This data has important implications in the care of the patient with CO₂ retention. Since the amino acid infusions are administered by peripheral vein this phenomenon may have a potential for broad application.

Our application to the Army last year referred to the data in the literature suggesting that normal subjects receiving only 5% dextrose by vein in amounts of approximately 100 gms per day will develop decreased ventilatory responses to hypoxia and perhaps to hypercarbia within 7 to 10 days. This year we have undertaken a study of 8 normal subjects with the dual objectives of confirming this finding and also of determining how rapidly an amino acid infusion might act to return the CO₂ response to normal, if it is indeed reduced. We have hospitalized 8 normal subjects who

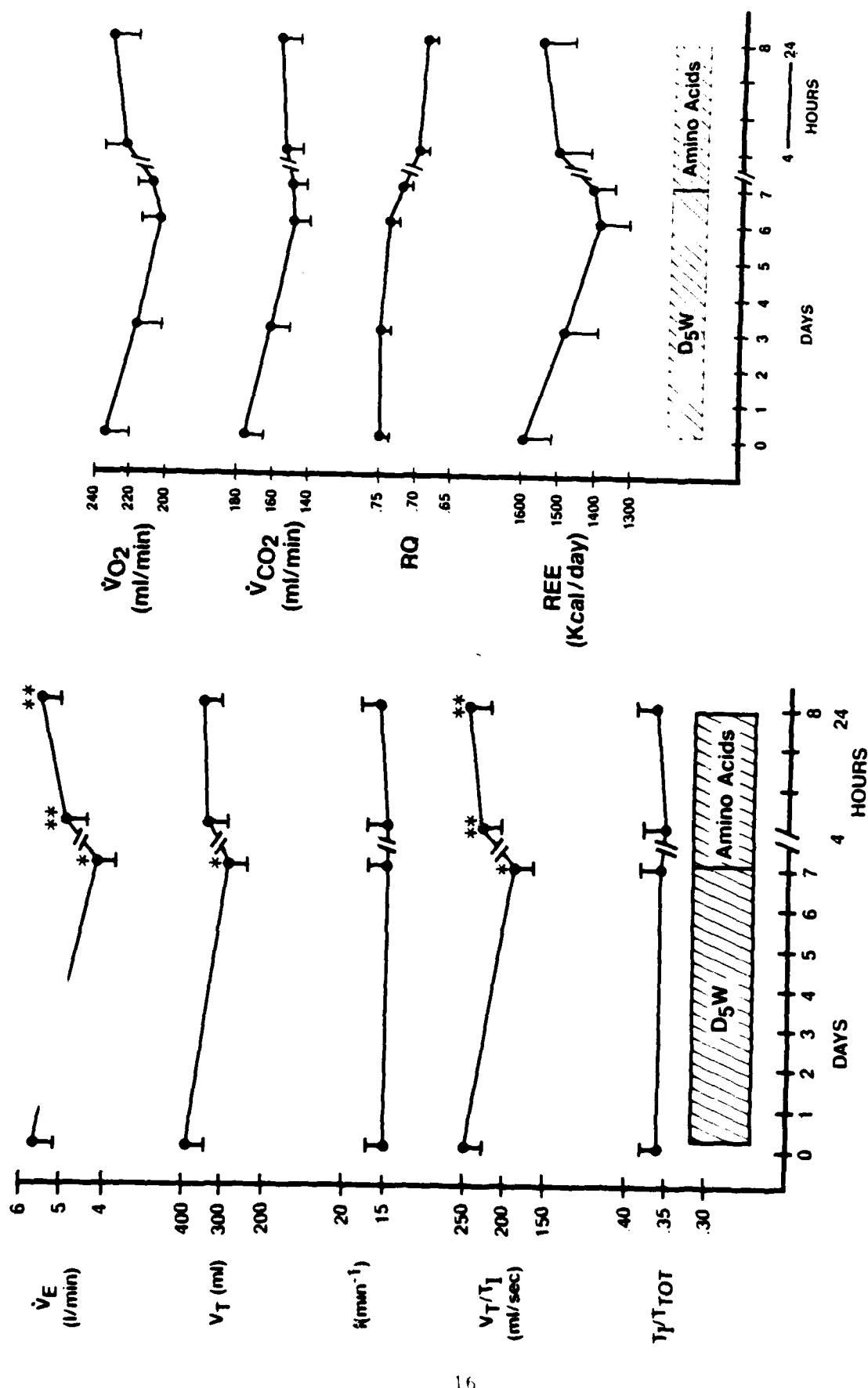


Figure 2

Figure 3

received approximately 100 grams of glucose a day as their sole nutrition for 1 week. At the end of that time they received an amino acid infusion for 24 hours. Gas exchange and ventilatory studies including the response to CO_2 were performed on Day 0, and Day 7 as well as after 24 hours of amino acid infusion. The subjects showed a distinct decrease in their resting energy expenditure during the week on 5% dextrose with a corresponding decrease in minute ventilation and tidal volumes (Figs. 2 &3). Amino acid infusion caused a return toward control values within 4 hours which was complete within 24 hours.

D. Use and calibration of commercial respiratory equipment. Measurements of O_2 consumption ($\dot{V}\text{O}_2$), CO_2 production ($\dot{V}\text{CO}_2$) and respiratory quotient (RQ) have been demonstrated to be important clinical parameters, particularly in patients with respiratory failure. Performing these measurements in patients receiving mechanical ventilation has proved difficult. Recently, two commercial instruments (Siemens-Elema Servo Ventilator 900B and Beckman Metabolic Measurement Cart) designed to perform measurements of gas exchange during mechanical ventilation have been introduced. However, the accuracy and reproducibility of these instruments remains to be evaluated. We examined the capabilities of these instruments and devised a simple model for initial testing and continued recalibration of instruments designed to perform gas exchange measurements.

In the initial phase both instruments were used to ventilate a lung model (Fig. 4). Gas exchange was reproduced by administration of CO_2 (to simulate $\dot{V}\text{CO}_2$) and N_2 (to simulate $\dot{V}\text{O}_2$). Flows of both gases were introduced into the system using Matheson flowmeters (601 for CO_2 and 603 for N_2) which were calibrated using a mercury-O-ring dry spirometer. Ventilatory conditions were varied (frequency = 10, 15, 10, tidal volume =

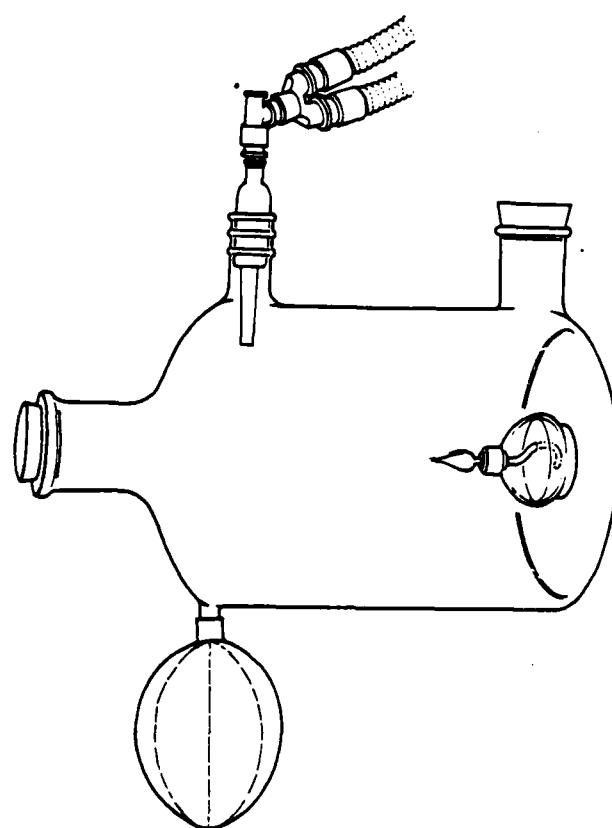


Figure 5

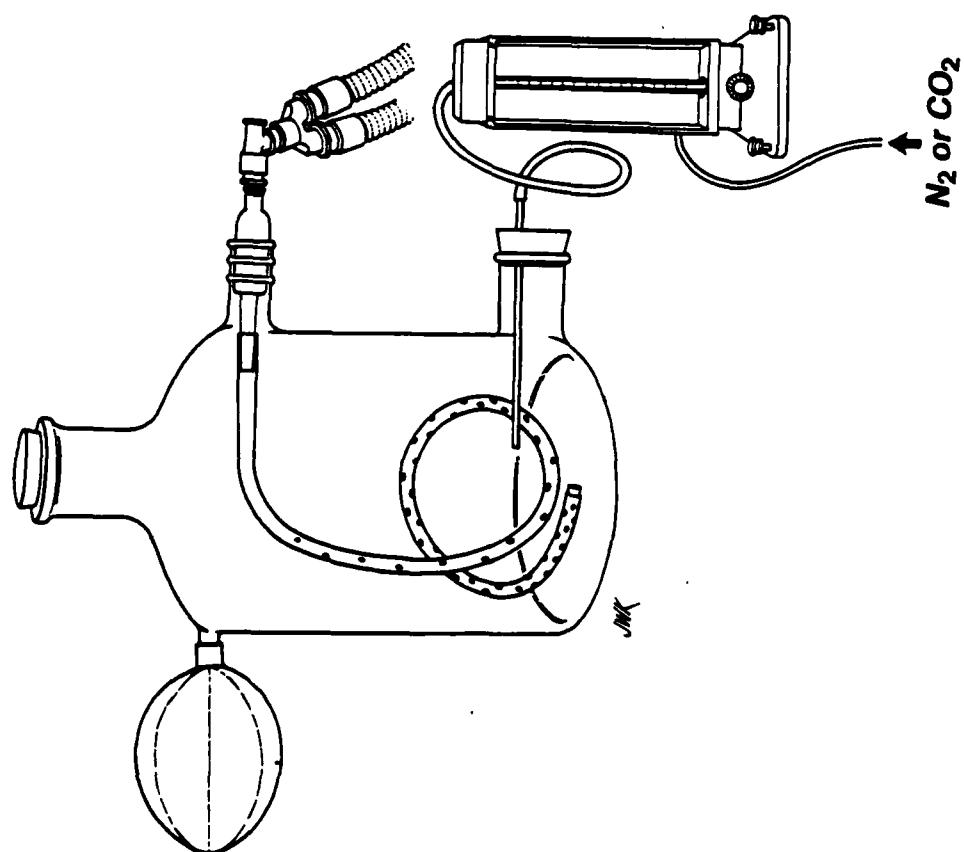


Figure 4

250, 333, 350, 466, 500, 666, 700 and 1000 ml, $\text{FIO}_2 = .21, .40, .85$) as were the simulated levels of gas exchange ($\text{VCO}_2 = 85 - 270 \text{ ml/min}$, $\text{VO}_2 = 80 - 933 \text{ ml/min}$). Each condition was studied for 8 minute periods on 4 occasions. In the second phase of the study the ability of the two instruments to measure RQ was assessed by burning methanol ($\text{RQ} = .67$) and ventilating the lung model as shown (Fig. 5).

Representative results using ventilatory parameters and levels of gas exchange that would be expected in an adult patient are shown in Fig. 6. At physiological tidal volumes for adults (466-700 ml) there was less than a 7% difference between measured vs administered CO_2 . With smaller tidal volumes (150-350 ml) the discrepancies widened to 13% and 10% respectively for the Siemens (S/E) and Beckman (B) systems respectively. Measured vs calculated O_2 consumption was within 10% and 5% for the S/E and B systems on room air. With increasing levels of FIO_2 the difference between measured and known RQ remained within 5% and 1.5% for S/E and B respectively.

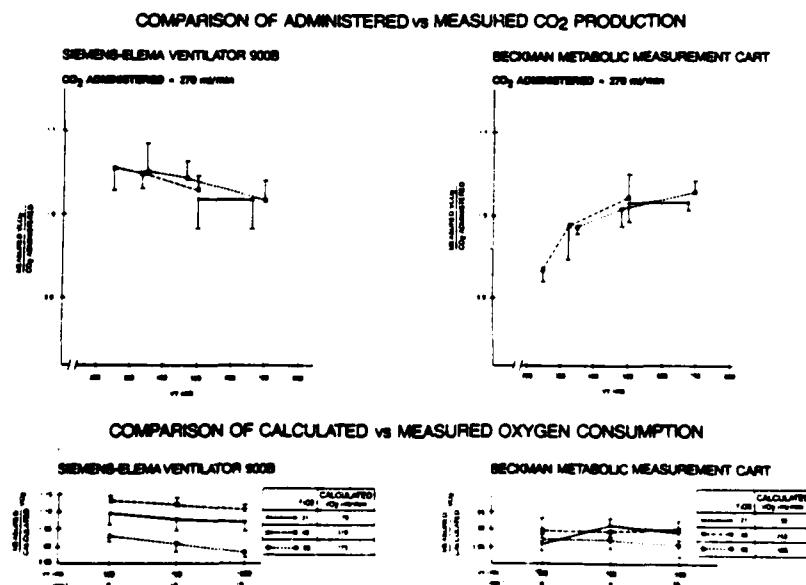


Figure 6

Thus both instruments give accurate and reproducible measurements of gas exchange as assessed by this in vitro testing system. This system appears to be useful for initial testing and continued validation of these instruments.

It is important to emphasize that both the S/E Servo Ventilator and the B Metabolic Measurement Cart are precision instruments that require careful calibration and continued maintenance. Both instruments, even when calibrated according to the specifications of the manufacturer, can periodically yield unreliable data. Thus a routine system for continued validation is mandatory.

III Muscle Composition.

A. Muscle water, electrolytes and glycogen. Prior studies from this unit (see progress report 1979-1980) have shown that muscle water, chloride and sodium increase after severe injury or during sepsis. This indicates an expansion of the extracellular compartment of muscle similar to that measured by whole body tracer studies.(1). These data, combined with data of Bergström, Fürst and Vinnars, collected in Sweden, are currently being prepared for publication. Other studies from this laboratory (2,3, Progress Report 1979-1980) have shown an interrelation between the effects of diet and injury on high energy phosphate compounds in muscle. Fasting normal subjects produces no change. Fasted patients, after total hip operation, have reduced concentrations of ATP and ADP and increased concentrations of AMP, however these changes are abolished by infusing 5% dextrose. Severely injured or septic patients show even bigger changes in high energy phosphates which are not abolished by 5% dextrose but are overcome with total parenteral nutrition. Thus with injury there are decreases in ATP and ADP and increases in AMP which are more marked with increasing severity. Glucose administration can

Table III. Muscle water electrolytes. Membrane potential set at 87.2 mv.

	Normal	Low Glucose	High Glucose
n	37	7	7
Water - ml/100 g FFS			
Total	333.4 ± 1.9	365.2 ± 12.1***	345.4 ± 11.4
Extracellular	45.7 ± 1.5	103.1 ± 20.2***	87.0 ± 18.8***
Intracellular	287.7 ± 2.4	262.1 ± 19.3**	258.5 ± 15.3**
Electrolytes - meq/100 g FFS			
Sodium	9.9 ± .3	14.0 ± 2.3**	11.6 ± 1.1
Potassium	45.8 ± .2	45.7 ± .2	44.2 ± .9**
Magnesium	8.4 ± .1	8.6 ± .1	8.4 ± .2
Chloride	6.5 ± .2	12.2 ± 2.2***	10.2 ± 1.9***
Electrolytes - meq/l IC water			
Sodium	11.7 ± 1.1	.4 ± 5.7_*	-.8 ± 6.2**
Potassium	158.9 ± 1.3	172.1 ± 13.6	171.0 ± 7.2**
Magnesium	29.1 ± .5	32.0 ± 2.5	32.3 ± 1.3*

Differs from normal, p<.05*, .01**, .001***

inhibit these changes, and is more effective as the amount increases. Since membrane potential is closely linked to ATP and ADP concentrations, and electrolyte and water distribution are in turn dependent on membrane potential, it seemed likely that diet and particularly glucose might affect the changes in water and electrolytes seen in injury and sepsis.

With these considerations in mind, a prospective study was initiated of the effects of low (550 kcal/day) and high (2100 kcal/day) glucose intakes on the changes in muscle water, electrolytes and glycogen induced by injury. Five severely injured patients (3 with gunshot wounds, 1 after a 5 story fall, and 1 postcystectomy) and 3 septic patients were maintained either for 3 days on the low intake followed by three days on the high intake, or vice versa. Muscle biopsies and blood samples were taken on the third day of each diet. Data for seven of the patients are given here. Compared to normal values these patients had significant increases for muscle water, sodium and chloride on the low glucose intake (Table III). On the high glucose diet the increases were smaller, only chloride showing a significant increase. There was a significant decrease in potassium on the high but not the low intake. These data suggest that high glucose may partially counteract the effects of injury, however with the small numbers used there was no significant differences between the high and low intakes by the paired t test.

The values for intracellular (ICW) and extracellular water (ECW) and for electrolyte concentrations in ICW have been calculated from the chloride data using the Nernst equation and assuming a normal membrane potential of 87.2 mv.(4) They indicate a marked expansion of ECW and contraction of ICW (Table III). However, it is unlikely that the membrane potential was not affected by the severe injury or sepsis. Furthermore the calculated decrease in IC sodium and increase in IC potassium concentrations are inconsistent with an unchanged membrane potential. It is not feasible to measure the membrane potential in these studies, however, various arbitrary values may

Table IV. Muscle water and electrolytes. Membrane potential set at 55 mv.

	Low Glucose	High Glucose
n	7	7
Water - ml/100 g FFS		
Total	365.2 ± 12.1	345.4 ± 11.4
Extracellular	75.3 ± 21.9	59.6 ± 20.0
Intracellular	289.9 ± 21.3	285.8 ± 16.9
Electrolytes - meq/l IC water		
Sodium	13.0 ± 5.1	12.0 ± 5.6
Potassium	156.1 ± 12.3	155.2 ± 6.5
Magnesium	29.1 ± 2.2	29.4 ± 1.2

be used in calculating ECW and ICW. When a membrane potential of 55 mv was used, IC sodium concentrations were increased and potassium concentrations were decreased from normal, qualitatively consistent with a reduced potential (Table IV). With this membrane potential, calculated values for ICW no longer differ from normal. However ECW values remain higher than normal and are higher on the low than the high glucose intake. It seems likely that, in these patients, there is both a change in membrane potential as well as an expansion of ECW.

Glycogen has been determined in muscle biopsies from the eight patients and from four normal subjects treated identically. In both groups there was a significant increase in glycogen content in going from the low to the high glucose intake (Table V). These changes are similar to those previously reported by Hultman. (5) The injured patients had lower muscle glycogen

Table V Muscle glycogen concentrations

	Low Glucose g glycogen/100 g fat free solids	High Glucose g glycogen/100 g fat free solids	Difference \pm SEM
Normals (n = 4)	4.7 \pm 1.0	6.4 \pm .6	1.7 \pm .5*
Injured/septic (n = 8)	3.1 \pm .7	5.9 \pm .5	2.8 \pm .3**

*p<.05, **p<.001

contents than the normals on the low diet and bigger increases in going to the high diet. However, these differences were of borderline significance and more studies are needed to confirm the findings.

We may conclude that increasing glucose intake increases glycogen content in injured/septic patients, possibly to a greater extent than in normal, and that this may be accompanied by partial prevention of the decreases in muscle membrane potential and increase in muscle ECW induced by injury or sepsis. More studies are planned for the coming year, both of normals and sick patients, to confirm these findings.

B. Muscle high energy phosphate compounds. During the past year the manual, enzymatic methods we were using for measurements of ATP, ADP, AMP, creatine, phosphocreatine, glucose-6-phosphate, and lactate in muscle biopsies have been adapted for use with a newly purchased Instrumentation Laboratories fast centrifugal analyzer. This permits more rapid and reproducible analyses on smaller amounts of material. No human studies were conducted during this period but we plan to resume them shortly.

C. Muscle concentrations of carnitine derivatives and of carnitine palmitoyl transferase. It has been suggested that part of the metabolic derangement seen in injury and sepsis may be due to an absolute or relative carnitine deficiency. Carnitine is required for transport of long chain fatty acids into mitochondria. A carnitine deficiency would lead to decreased ability to oxidize fat and increased reliance on protein and glucose for energy, and might help to explain the increased nitrogen losses in injured or septic patients. Border et al (6) have demonstrated that carnitine concentrations are reduced in sepsis in both man and dog.

With this in mind we have initiated a study of the effect of injury, sepsis and diet on muscle concentrations of free carnitine, carnitine esters, and the enzyme, carnitine palmitoyl transferase (CPT). During the past six months, methods for measuring these compounds (7,8,9) in open biopsies have been modified to permit accurate analysis in the small amount of tissue (ca 50 mg) which can be obtained with the noninvasive needle biopsy technique which we are using for measuring muscle water, electrolytes, glycogen, high energy phosphates and amino acids (10). These modifications have been completed and studies are now in progress on the effects of high and low glucose intakes in normal subjects and in injured or septic patients.

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